tazidime against inducible Gram-negative isolates, and comparable activity to ceftazidime against *Pseudomonas aeruginosa*.

Conclusion: Fourth generation cephalosporins are highly potent agents, but continued surveillance is mandatory.

S182 Antimicrobial surveillance programmes

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Currently, prevalence rates for nosocomial infections range between 5% and 17% of patients admitted to hospitals. The control of nosocomial infections has been well recognised as a major priority in the hospital setting. Components for controlling nosocomial infections in the hospital include antibiotics, which hold a rather ambivalent position: empirically used, antibiotics may select for resistant bacteria. It is important to target the micro-organism and limit the spread of resistant bacteria. Antimicrobial surveillance programmes are unique tools to detect and identify dangerous micro-organisms and to optimise the use of empiric antibiotic therapy. A variety of surveillance programmes have been developed. Enhancements in surveillance have been related to improved sampling, accurate clinical information, quantitative methods of susceptibility testing, quality control measures in the laboratory, as well as interpretation of the results. The database of detailed information can be analysed with the appropriate software. The results can them be compared to information gathered ate other institutions, on regional, national and global bases.

S183 Informed decisions in an era of resistance

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Antimicrobial resistance is increasing worldwide. Recent increases in β-lactam resistance amongst Gram-negative bacteria such as *Enterobacter cloacae*, *Citrobacter freundii*, and *Pseudomonas aeruginosa* have been linked to use and overuse of ater-generation cephalosporins. Further resistance emergence may be delayed or reduced through the use of newer agents, combination therapy, and antibiotic cycling. In vitro data suggest that the fourth-generation cephalosporins are generally more potent than, and select less resistance than previous agents. Initial clinical data, though yet sparse, suggest that substitution of these agents for their predecessors, particularly when in combination with aminoglycosides, results in lower resistance rates. While clinical trials, due to their design, have shown drugs such as cefepime to be at least comparable to the third-generation cephalosporins, superiority of the fourth-generation agents is indicated in selected cases of infection with Bush group 1 enzyme-producing bacteria. This superiority is at least partially due to the low inducing potential for the group 1 enzymes, rapid permeation characteristics and resistance to hydrolysis. Organisms like *E. cloacae* can become resistant to third-generation agents through a single mutational step, while two mutations are required for resistance to the fourth-generation drugs. Adoption of practices and agents that reduce the selection of resistance may extend the useful lives of our current drugs, and may also delay the onset of the "post-antibiotic era".

S184 Empiric Therapy: Algorithms for Success

J. Carlet. *F*

No abstract available.

S185 Management strategies for infection in the neutropenic patient

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Neutropenic patients are susceptible to severe and prolonged infection. Empiric therapy to prevent it has traditionally been designed to cover Gram-negative rods, especially *P. aeruginosa*, which were the most likely bacterial pathogens. Over the past two decades however, Gram-positive infections have progressively become a more common cause of sepsis in neutropenic patients, now accounting for 70% of infections. Adequate coverage against Gram-negative organisms remains nevertheless mandatory. It is performed usually with a combination of antibiotics but recently introduced antibiotics like cefepime and meropenem have been used successfully as a monotherapy. These agents have an excellent antipseudomal activity, they are synergistic with aminoglycosides and, moreover, are effective against many streptococci and methicillin-sensitive staphylococci. Vancomycin or teicoplanin are only indicated in the presence of a resistant organism, most commonly *Staph. epidermidis*. The addition of amphotericin B is indicated after 96 hours if the patient remains neutropenic and febrile, and the initial microbiological workup has been negative. This is especially the case in patients with severe neutropenia and/or a newly apparent clinical site of infection. The suspicion of fungal infections should be even higher in neutropenic patients who are immunosuppressed, such as those with graft-versus-host disease after allogeneic bone marrow transplantation. In those patients, cytomegalovirus and other vital infections should be looked for and treated early. Colony stimulating factors can effectively shorten the duration of neutropenia and can be used as an adjunct to antibacterial and antifungal agents when neutropenia is severe and the control of infection is not optimal.

Endothelium and microbial interactions (Joint Symposium with the Infectious Diseases Society of America)

S186 Endotoxin Influences Endothelial Barrier Function

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Gram-negative septic processes can be complicated by vascular leak syndromes, including the adult respiratory distress syndrome. The bacterial component responsible for much of the endothelial cell (EC) injury and dysfunction is the bacterial lipopolysaccharide (LPS). Although LPS induces numerous host mediators of EC injury, evidence also exists for a direct role for LPS. LPS, in concert with the accessory molecules LPS-binding protein (LBP) and soluble CD14, directly interacts with the vascular EC to induce loss of barrier function through the paracellular pathway. The molecular basis for this LPS-EC interaction and the resultant EC response have not been defined. A specific binding site/receptor for LPS on the non CD14-bearing EC, although implied, has not been demonstrated.

We now know that LPS induces tyrosine phosphorylation of a cytoskeletal protein, paxillin, and that protein tyrosine kinase inhibition protects against opening of the EC paracellular pathway in response to LPS. The phosphotyrosine-containing proteins in LPS-exposed EC can be immunolocalized in part, to the intercellular boundaries.

The LPS-induced endothelial barrier dysfunction also appears to be mediated through actin reorganization. LPS induces EC actin depolymerization and prior F-actin stabilization with phallicidin pro-

tects against the loss of barrier function. The LPS-induced actin reorganization is also tyrosine phosphorylation-dependent.

Conclusions: LPS directly influences endothelial barrier function through tyrosine phosphorylation-dependent actin reorganization and opening of the paracellular pathway.

S187 Effect of Bacterial Exotoxins on Endothelial Functions

W. Seeger. D

No abstract available.

S188 Microbial-Leukocyte-Endothelial Cell Interactions and Altered Permeability of the Blood-Brain Barrier during Meningitis

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Bacterial meningitis (BM) is characterized by the presence of polymorphonuclear neutrophils (PMNs) within the subarachnoid space. Evidence indicates that high cerebrospinal fluid concentrations of PMNS contribute significantly to the poor outcomes resulting from BM. Much of the research being conducted BM has focused on the identification of host factors that may contribute to this process.

Interactions between bacteria, PMNs, and the cerebral microvascular endothelial cells (CMVECs) that comprise the blood-brain barrier likely play a significant role in the generation of the host inflammatory response and in the development of the pathophysiologic events that occur during BM. Exposure of CMVECs to certain bacterial components or to endogenous proinflammatory mediators stimulates production and release of factors that are chemotactic for and/or activate PMNs. Increased expression and avidity of leukocyte-endothelial cell adhesion molecules on PMNs and on CMVECs facilitate localization and transendothelial migration of PMNS. Bacteria, PMNs, and their products may also have deleterious effects on CMVECs, thus compromising the integrity of the blood-brain barrier and the ability of the CMVECs to maintain homeostasis within the central nervous system. Advances in the understanding of these interactions may help to identify targets to direct agents that may be used in the adjunctive therapy of BM.

S189 Endothelial Lesions in Malaria

G.E. Grau. *CH*

No abstract available.

Influenza and pneumococcal vaccination for older adults in Western Europe

S190 The Epidemiology of Influenza and Pneumococcal Infections

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Due to antigenic drift influenza A and B viruses usually cause epidemics of influenza in Europe and elsewhere 5–6 times over a 10-year period. Antigenic shift in influenza A virus may cause changes that make most of the worlds population susceptible leading to influenza pandemics. This happened in 1900, 1918 ("The Spanish flu"), 1957 (Asiatic flu), 1968 (Hong Kong flu) and possibly in 1995. In Denmark with a population of little over 5 mio, influenza epidemics led to an excess mortality of 1400 in 1989/90, of 2000 in 1993/94 and of 2800 in 1995/96. So, obviously, there is much to be obtained by prevention.

Over the last twenty years the number of cases of invasive pneumococcal disease has increased ten times in Denmark – as well as reportedly in Norway. The incidence was 20 cases per 100,000 inhabitants in 1995 and the highest rates were seen in the very young (23/100,000) and in the elderly (55/100,000). The ten first types in order of frequency represented 65% of all isolates from patients of all ages and as many as 85% of isolates from children with some variation as to which types actually were the ten most common over the years.

Types present in the currently available 23-valent pneumococcal polysaccharide vaccines over the last 20 years have covered ca. 90% of all invasive disease isolates in most countries and in all age groups.

S191 The Clinical Effectiveness, Cost-Effectiveness and Implementation of Influenza Vaccination

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Several studies have shown that influenza vaccines prevent 60 to 90% of natural-occurring influenza virus infections in adults. Among the elderly, influenza vaccination prevents 30 to 60% of influenza-related hospitalizations, and 30 to 54% of all-causes mortality. Additional studies have shown that the cost-effectiveness of influenza vaccination exceeds that of almost all other preventive, screening and treatment measures used in the care of older persons. In the Netherlands, a recent cost-effectiveness study led public health authorities to modify their policy and to include age $\geq$65 years as an indication for influenza vaccination. Currently, only four Western European countries have influenza vaccination policies that target only at-risk persons. Not surprisingly, great differences still exist among these countries in their use of influenza vaccine, in 1995 the number of doses distributed ranged from 48 to 170 doses per 1000 total population. The reasons underlying the persistent variations in vaccine use remain poorly understood. With this in mind, the European Scientific Working group on Influenza (ESWI) has initiated several socioeconomic studies of influenza and undertaken surveys on surveillance and diagnostic methods, immunization rates, and educational programs for health care providers and the public. The goal of these studies is to improve the implementation of influenza immunization policies throughout Europe.

S192 The Clinical Effectiveness, Cost Effectiveness and Implementation of Pneumococcal Vaccination

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Pneumococcal infections are a major cause of morbidity and mortality in adults resulting in increased costs to the health care sector as well as to the individual. Clinical trials and observational studies (both case control and retrospective cohort designs) have examined the efficacy and effectiveness of vaccination in older individuals. Clinical trials have failed to show efficacy against pneumococcal pneumonia largely because of methodological problems or unrepresentative sample populations. The observational studies however have shown a clinical effectiveness of 50 to 70% in preventing invasive pneumococcal disease. Cost effectiveness studies conducted in the United States and more recently in The Netherlands and Spain sugest suggest vaccination of older people (over 64 years) to prevent pneumococcal pneumonia would be worthwhile, and a recent study from the US has shown that vaccination to prevent pneumococcal